MEDICAL STAFF CONFERENCE

Edema Formation and the Use of Diuretics

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SLEISENGER:* There are a number of pathological disorders characterized by generalized retention of fluid and a need for removing this fluid from the body. In this regard, of course, the diuretic agents are in the forefront of therapeutic considerations. Dr. Earley will discuss the indications and the use of diuretic agents.

DR. EARLEY:† I would like to begin with a discussion of factors which appear to be involved in the regulation of sodium excretion and how these mechanisms may operate abnormally in the presence of a disease characterized by sodium retention and the formation of edema or ascites. I will then discuss the role diuretic agents may play in the reversal or amelioration of the pathogenesis of sodium retention and point out some of the important complications of diuretic therapy.

Chart 1 is a schematic summary of the major factors apparently involved in the normal regulation of sodium excretion. An increased dietary intake of sodium is followed by thirst and a release of antidiuretic hormone which leads to retention of the ingested water. In this manner the increment in dietary sodium is accompanied by the retention of an isotonically equivalent volume of water which expands the extracellular fluid (ECF) volume. This expansion of ECF initiates an increased renal excretion of sodium which will continue until the increment in dietary sodium is eliminated.[1]

Several factors seem to be involved in linking the expansion of ECF to increased excretion of sodium. One of these could be increased glomerular filtration rate (GFR) which would provide a larger amount of sodium and water for tubular reabsorption. If such an increased filtered load of sodium exceeds the existing reabsorptive capacity of the tubules, the surfeit will spill over into the urine.

Another factor effecting an increased excretion of sodium is a decrease in the secretion of aldosterone. Suppression of aldosterone secretion known to result from an increased intake of so-

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dium, would decrease the rate of tubular sodium reabsorption and permit more of the filtered sodium to escape into the urine. There is an increasing amount of evidence that intrarenal hemodynamic changes are involved in the regulation of tubular sodium reabsorption. These changes include an effect of decreased renal vascular resistance or increased renal perfusion pressure to lower the rate of tubular sodium reabsorption, possibly as a consequence of increased peritubular capillary hydrostatic pressure and a lowered rate of capillary absorption.

Finally, there is some evidence that there may be a hormone which is released in response to expansion of ECF volume and suppresses tubular sodium reabsorption. The renal tubular effects of such a hormone would be opposite to those of aldosterone.

Thus, as illustrated in Chart 1, there may be at least four categories of factors involved in the regulation of sodium excretion in response to changes in ECF volume.[2] It is likely that under normal conditions none of these pathways alone dictates the regulation of the sodium balance. Experiments have been designed in which filtration rate is controlled at a depressed level, yet the kidney still increases sodium excretion in response to increased ECF volume.[3] When changes in aldosterone activity are avoided, either by adrenalectomy and replacement of hormone, or by providing excessive amounts of the hormone, the kidney still will eventually achieve sodium balance.[3,4,5] A similar lack of pre-eminence is probably true for the other specific factors influencing sodium excretion, and these multiple mechanisms undoubtedly work in concert, overriding each other when necessary to maintain volume integrity of the extracellular compartment. Just as neither mechanism alone determines the normal regulation of sodium excretion, it is likely that neither one alone accounts for sodium retention and edema formation in disease states.

Chart 2 is a schematic representation of abnormalities in fluid distribution and sodium excretion that may occur in congestive heart failure. I would like to emphasize that there are two somewhat independent mechanisms at play, one behind the heart and one in front of the heart. More than three decades ago Harrison[6] championed the concept of backward heart failure, which proposed that in right heart failure a major factor leading to sodium retention was increased venous pressure resulting from the inability of the heart to handle the venous return. The increased venous and capillary pressure should lead to a redistribution of extracellular fluid from the vascular compartment into the interstitial spaces. It was proposed further that increased renal venous pressure somehow resulted in sodium retention by the kidney. A short time later Warren and Stead[7] emphasized the concept of forward heart failure, which proposed that inadequacy of the arterial circulation leads to sodium retention and edema formation as a result of some unspecified effect on renal hemodynamics.

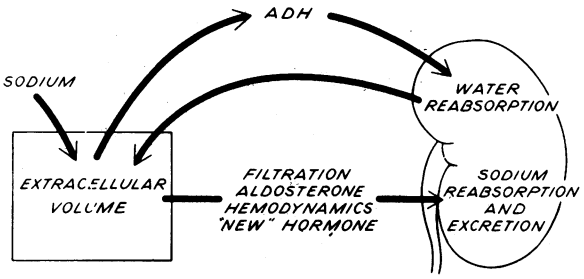

Chart 1.—Factors involved in the interrelationship between extracellular fluid volume and sodium excretion.

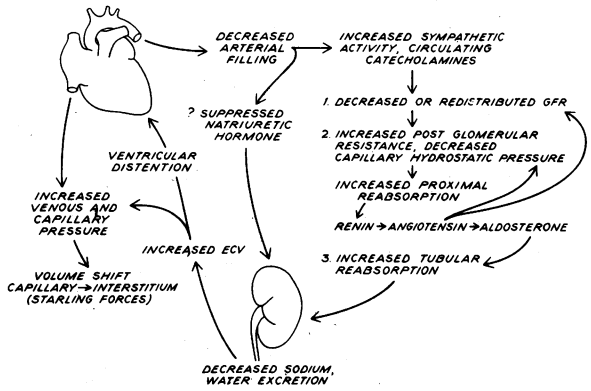

Chart 2.— Possible sequence of events associated with increased sodium reabsorption and edema formation in low-output cardiac failure.

In view of what appears to be "the light" of current knowledge, it seems reasonable to incorporate the fundamental features of both "backward" and "forward" heart failure into a modernized scheme for sodium retention and edema formation.[2] Failure of the heart as a pump results in increased venous and capillary hydrostatic pressure, with the highest pressures in the most dependent portions of the body. The in-

creased capillary hydrostatic pressure will cause a redistribution of volume from the vascular compartment to the interstitium as a result of redirection of the Starling forces operating across capillary walls. A similar redistribution of extracellular fluid may be an important feature of edema formation in other diseases, although there need not be an increase in capillary hydrostatic pressure. In the nephrotic syndrome, hypoalbuminemia results in a pronounced decrease in plasma colloid osmotic pressure, and this would produce a shift of volume between capillary and interstitium which is qualitatively similar to that resulting from increased capillary hydrostatic pressure. In liver disease with ascites, there is increased portal venous and capillary pressures and usually decreased plasma albumin resulting from underproduction by the diseased liver. This combination of altered Starling forces results in localized extravascular accumulation of fluid in the form of ascites.[8] Thus, the formation of edema or ascites may begin as a purely local phenomenon due to changes in the capillary beds specifically affected by the underlying disease.

Returning to the example of heart failure shown in Chart 2, one notes there is another, somewhat unrelated, influence of the diseased heart on sodium balance. When the heart fails as a pump, there is an inadequate circulatory output, sometimes described as "decreased arterial filling" or "decreased effective ECF."[9] An inadequate cardiac output results in several changes that could affect sodium excretion. Activity of the sympathetic nervous system is increased, and very likely so are circulating catecholamines. Such increased sympathetic activity, either through direct renal innervation or as a result of circulating catechols, may account for the increased renal vascular resistance usually present in heart failure.[10] Retention of sodium would be favored by the resultant decreased GFR or possibly by a redistribution of filtrate to nephron populations of maximal reabsorptive capacity.[11] In addition, increased renal vascular resistance should decrease hydrostatic pressure in the peritubular capillary circulation, a change that may enhance proximal tubular sodium reabsorption.[2] Increased proximal tubular reabsorption diminishes delivery of sodium to more distal parts of the nephron, and this decreased delivery may trigger the juxtaglomerular apparatus to increase the output of renin.[12] Increased plasma renin will lead to increased formation of angiotensin from plasma alpha-2 globulin; and angiotensin has two recognized actions, both of which could decrease sodium excretion.

The vasconstricting effect of angiotensin may decrease GFR and augment tubular sodium reabsorption as a consequence of decreased peritubular capillary hydrostatic pressure.[2] In addition, angiotensin stimulates the secretion of aldosterone,[13] and the latter hormone has a direct effect to increase tubular sodium reabsorption. In this scheme the forces promoting the accumulation of extravascular fluid are located behind the heart in the venous and capillary circulation, and the forces promoting renal sodium retention are localized in front of the heart in the arterial circulation.

The kidney may be regarded as responding in an appropriate manner to what it perceives as an inadequate arterial circulation. In this sense the retention of sodium may be looked upon as an effort of the kidney to replenish the ECF and to compensate for the failure of the heart to provide an adequate circulation. However, the failing heart is not inclined to accept the expanded ECF so generously provided by the kidney, since it already may be pumping the venous return at maximum capacity. This compensatory expansion of ECF volume will further increase venous and capillary pressures so that much of the retained fluid would be translocated into the interstitium in the form of more edema or ascites or both. To the extent that the retention of sodium and water expands the vascular volume and produces ventricular distention, there may be further decompensation of the heart as cardiac output falls along the descending limb of Starling's curve.

Where, if anywhere, do diuretics enter therapeutically into this scheme of heart failure? By forcing the excretion of sodium and decreasing extracellular fluid volume, venous and capillary pressures may decrease, this decrease resulting in the movement of edema fluid from the interstitium into the vascular compartment. Perhaps more important, cardiac output may increase to the extent that ventricular distension is diminished by forced diuresis. Thus, a desirable therapeutic result of diuretics may be achieved by reversal of some of the pathogenetic mechanisms in heart failure. However, this gratifying sequence of events may not always occur; and in some instances forced diuresis may not increase cardiac

output,[14] but instead may worsen the circulatory status.

As mentioned above, edema formation in the nephrotic syndrome relates primarily to diminished plasma albumin. Decreased plasma protein osmotic pressure initiates the formation of edema by translocating fluid from the vascular to interstitial compartment, and vascular volume generally is decreased in the nephrotic syndrome. Therefore, the stimuli initiating sodium retention are analogous to those produced by bleeding the normal individual. In a patient with hypoalbuminemia, "bleeding" into the interstitial spaces should activate the sequence of events leading to sodium retention as shown for heart failure in Chart 2.

In the case of cirrhosis of the liver, or other liver diseases characterized by the accumulation of ascites, the sequence of events leading to sodium retention is more difficult to formulate. It seems well established that cardiac function (output) may not be compromised in patients with liver disease and ascites.[15,16] It would seem possible, if there were not evidence to the contrary, that the formation of ascites (related to local forces in the portal circulation) could deplete the circulating volume and initiate sodium retention. However, in cirrhosis of the liver, cardiac output is usually normal or increased and the intravascular volume may be expanded.[16] In many patients with cirrhosis and ascites, blood pressure is often low in spite of increased cardiac output, indicating pronounced peripheral vasodilatation, but renal vascular resistance is often quite high.[16,17] It is possible that a generalized decrease in peripheral vascular resistance may lead secondarily to neural or neurohumoral renal vasoconstriction, and the latter change may account, at least in part, for sodium retention.

With this survey of the pathogenesis of edema as a background, I would like to turn now to a discussion of diuretic agents. Chart 3 illustrates the sites along the renal tubule where sodium reabsorption occurs through functionally different mechanisms and where the major classes of diuretic agents appear to exert their effects.[18,19,20] In the proximal tubule approximately 70 percent of the filtered sodium is reabsorbed isotonically. Another 20 percent is reabsorbed in the medullary portion of the ascending limb of Henle's loop; 5 to 10 percent is reabsorbed in the more distal cortical part of the loop of Henle; and finally some-

TUBULAR SITES OF SODIUM & WATER REABSORPTION

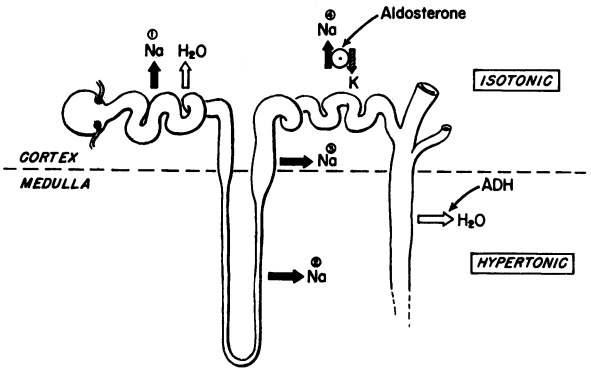

Chart 3.—Renal tubular sites of sodium reabsorption action of diuretic agents.

thing less than 5 percent of the filtered sodium is reabsorbed in the distal nephron under the stimulation of aldosterone. At this aldosterone-sensitive distal tubular site there is a reciprocal relationship between sodium reabsorption and potassium secretion. From a quantitative point of view, if a diuretic agent extensively interfered with sodium reabsorption in the proximal tubule it could affect the excretion of up to 70 percent of the filtrate. In terms of normal glomerular filtration rate, this would be the excretion of approximately 100 liters of urine a day.

Fortunately, the pharmaceutical industry has not yet developed a diuretic agent that will extensively block sodium reabsorption throughout the proximal tubule, for such a drug would be a very hazardous one. Interference with reabsorption in the early part of the ascending limb of Henle should result in excretion of 20 to 30 percent of the filtered sodium, and it is this site of tubular reabsorption at which ethacrynic acid appears to exert its effects. Ethacrynic acid thus may result in the excretion of 20 to 25 percent of the filtered sodium when administered in optimal doses. If this excessive blockade of tubular reabsorption were sustained for long periods, severe complications could occur. Five percent of the filtered sodium appears to be reabsorbed at a slightly more distal site in the cortical portion of the ascending limb, and it is at this site that thiazide diuretics interfere with sodium reabsorption. Furosemide appears to block reabsorption throughout the length of the ascending limb and possibly to a lesser extent in the proximal tubule,

overlapping the sites of action of ethacrynic acid and thiazides. Ethacrynic acid and thiazides have additive effects to promote the excretion of sodium,[21] and because of these separate tubular sites of action there is a physiological basis for combining the two agents therapeutically. Ethacrynic acid and furosemide would not be an intelligent combination of diuretic agents since both exert their major effects at the same tubular site.[22]

Agents that block the distal tubular mechanism, where aldosterone stimulates sodium reabsorption and leads to postassium secretion, promote the excretion of only 1 to 2 percent of the filtered sodium. Therefore, the aldosterone antagonist, spironolactone, is a relatively weak diuretic agent when administered alone.[19] The same should be true for triamterine, which interferes with sodium reabsorption at the same tubular site. However, triamterine is not an aldosterone antagonist, and it will decrease sodium reabsorption independent of aldosterone activity. In contrast, the natriuretic effect of spironolactone occurs only in the presence of aldosterone-stimulated sodium reabsorption.[23] Spironolactone and triamterine are most effective when used in combination with another diuretic agent that blocks sodium reabsorption at one of the more proximal tubular sites. For example, combining a thiazide with spironolactone or triamterine can result in a complementary effect of the two agents to promote the excretion of sodium, possibly at rates in excess of that achieved with either of the two drugs alone.[19] Such an additive effect should occur also when ethacrynic acid is administered in combination with an aldosterone antagonist or triamterine.

The relative power of various diuretic agents is shown in Table 1.[19] Here organomercurials have been assigned a power of 1 and are used as a standard for comparing the natriuretic power of other agents. Under optimal experimental conditions, organomercurial diuretics will block the reabsorption of approximately 20 percent of the filtered sodium. By comparison furosemide is almost twice as powerful; ethacrynic acid is about one and a half times as powerful; thiazides are approximately one-fourth as powerful; and spironolactone and triamterine may be at best only approximately one-tenth as powerful as organomercurials.

When administered in optimal dosage, the numerous thiazide derivatives are equal in terms

TABLE 1.—*Relative Power of Commonly Used Diuretics*

Organomercurials	1*
Furosemide	2
Ethacrynic Acid	1.5
Thiazides	0.25
Triamterene	0.10
Spironolactone	0.10

*Under optimal experimental conditions organomercurial diuretics may result in the excretion of about 20 percent of the filtered load of sodium. The power of the other diuretic agents, determined under similar conditions, is expressed relative to that of organomercurials.

of their ability to interfere with sodium reabsorption.[19] Any alleged difference in power among the thiazide diuretics refers to the size of the dose required to achieve a maximal effect. However, even when 2 grams a day is necessary to achieve a maximal natriuretic effect, as is the case with chlorothiazide, the patient can easily tolerate this small amount of medication. Also, all of the thiazide derivatives increase urinary potassium excretion to approximately the same extent.[18,19] The major difference among the various thiazides is found in the duration of action. Chlorothiazide is cleared by the kidney at a very rapid rate, and its duration of action is limited to two to four hours,[18] requiring a schedule of administration every four to six hours. Hydrochlorothiazide has an intermediate duration of action; and, at the opposite extreme, chlorthalidone has a duration of action of 48 to 72 hours.[18] Such prolonged action can be a disadvantage, since patients may forget to take a pill which is required only every second or third day.

The mechanism whereby diuretics increase the excretion of potassium involves an increased rate of delivery of sodium and water to the distal tubular site where sodium reabsorption leads to potassium secretion. Any diuretic agent that blocks reabsorption proximal to this distal tubular site has the potential to increase the secretion and excretion of potassium. Furosemide, ethacrynic acid and all the thiazides interfere with sodium reabsorption in the ascending limb, proximal to the distal tubular site of potassium secretion, and thereby lead to increased reabsorption of sodium in "exchange" for secreted potassium.[19] Thus, these agents are associated with increased excretion of both sodium and potassium. Furosemide and ethacrynic acid have been considered to be relatively potassium-sparing drugs since the ratio of excreted sodium to excreted potas-

sium is high. This results entirely from the extensive natriuretic effect of these two agents and not from a sparing of potassium excretion. In absolute terms, renal potassium wasting may be a prominent effect of treatment with furosemide and ethacrynic acid as well as with thiazides.

The extensive natriuretic effect of diuretic agents discussed earlier was determined under optimal experimental conditions, and such power is not encountered in most clinical situations. Table 2 lists factors that will reduce the natriuretic effect of diuretic agents.[19] A reduced GFR will decrease the amount of sodium presented for tubular reabsorption and, therefore, the amount of sodium that can be blocked from reabsorption by a diuretic. Filtration rate is often reduced in diseases characterized by edema. Moreover, filtration rate may fall further as a result of previous diuresis and contraction of ECF volume.

A second factor limiting diuretic activity is that diseases characterized by edema formation appear to be associated with increased fractional sodium reabsorption in the proximal tubules, a site where the diuretic agents exert little or no net effect. Thus, increased proximal sodium reabsorption in edematous states would limit the amount of sodium reaching distal tubular sites where diuretic agents block sodium reabsorption. In the case of organomercurial diuretics, hypochloremic alkalosis limits the pharmacological effect on sodium reabsorption. However, acid-base disturbances have little influence on the action of thiazides, furosemide or ethacrynic acid.

Finally, increased aldosterone activity, common in edematous states, promotes distal tubular reabsorption of sodium in "exchange" for secreted potassium. Thus, diuretics that act proximal to this distal tubular exchange site, may have their natriuretic effect blunted and kaliuretic effect enhanced as sodium is recaptured downstream by aldosterone-stimulated reabsorption.[19] This is the situation in which the aldosterone antagonist, spironolactone, would exhibit greatest natriuretic activity.

Chart 4 illustrates escape from the natriuretic effect of hydrochlorothiazide.[24] This study was performed in a patient with nephrogenic diabetes insipidus, and therefore the concentration of electrolytes in urine was not influenced by fluctuations in changing levels of antidiuretic hormone.[24] On the day the thiazide diuretic was begun there was an increased concentration of electrolytes in the urine, predominantly resulting from increased sodium concentration. During the ensuing three to four days there was a gradual decrease in the concentration of sodium in the urine without a fall in the total electrolyte concentration. The decreased concentration of sodium was accompanied by an increased concentration of potassium. By the fourth day of diuretic therapy, urinary sodium concentration was below the level present before administration of the drug, and there was a decided increase in potassium concentration. That this reversal of electrolyte composition of the urine was due to increasing aldosterone activity was suggested by the effect of spironolactone to reduce sharply the concentration of potassium and increase the concentration of sodium to similar levels as observed on the first day of thiazide therapy. This is, therefore, a situation in which the use of a combination of diuretic agents is appropriate and effective. It is probably unwise, however, to rely on prepared combinations of thiazides and spironolactone to produce the natriuretic effect illustrated in this example. Instead, the sodium and potassium content of the urine should be examined, and on this basis the decision to add an effective

TABLE 2.—*Mechanisms of Escape from the Natriuretic Effects of Diuretic Agents*

Decreased GFR
Increased Proximal Tubular Reabsorption
Increased Aldosterone Secretion
Enhances Distal Sodium Reabsorption
Enhances Potassium Secretion and Excretion
Hypochloremic Alkalosis
(Mercurial Diuretics Only)

TABLE 3.—*Some Important Complications of Diuretic Agents*

Potassium Depletion (Most Agents)
Potassium Retention (Spironolactone, Triamterene)
Hypovolemia (Any Agent)
Decreased GFR, Oliguria
Hyponatremia
Acidosis (Carbonic Anhydrase Inhibitors)
Alkalosis (Most Agents)
Carbohydrate Intolerance (Thiazides, (?) Furosemide)
Hyperuricemia (Most Agents)
Nephrotoxicity (Organomercurials)
Sensitivity Reactions (Any Agent)
Nerve Deafness (Ethacrynic Acid, Furosemide)

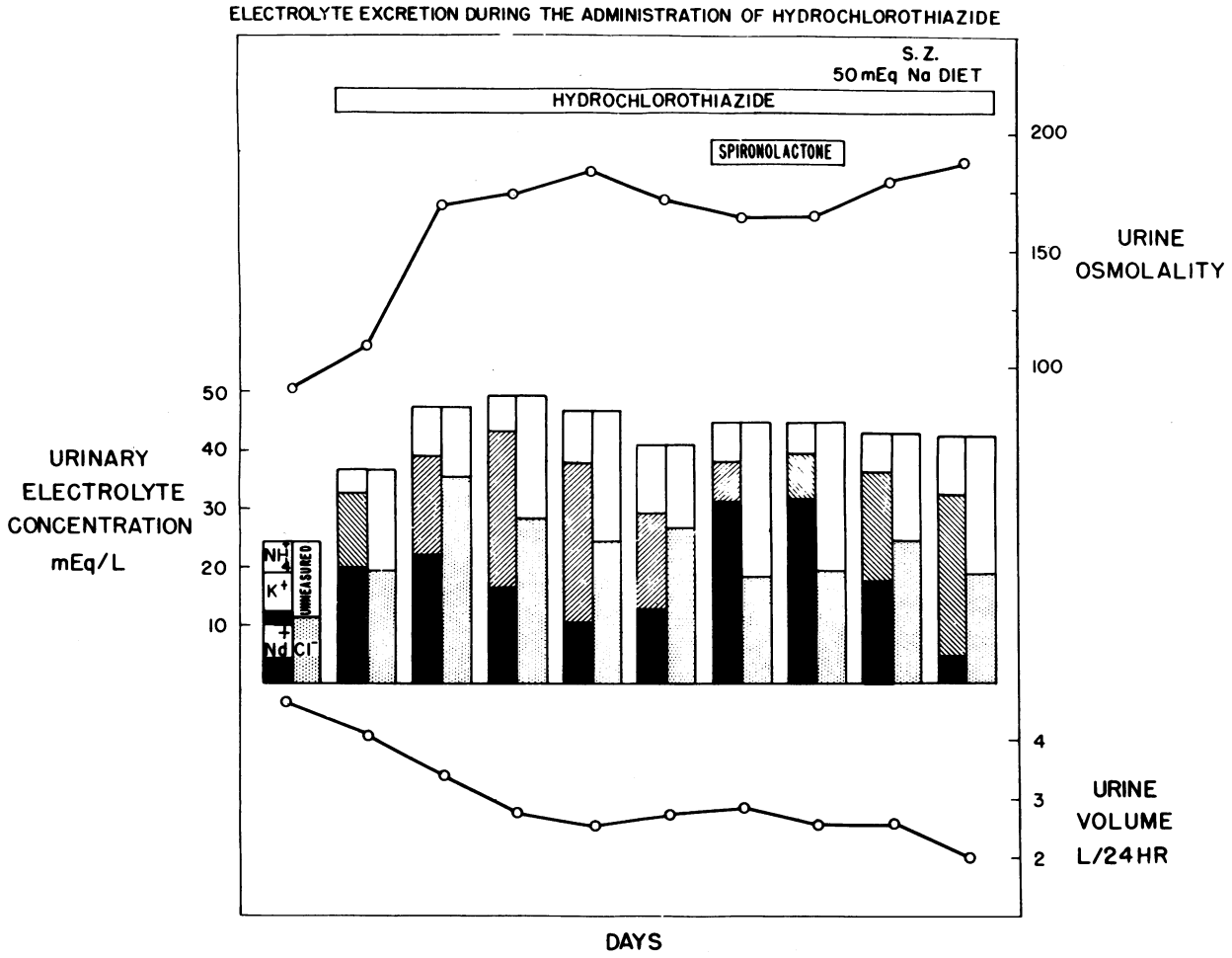

Chart 4.—Attenuation of natriuresis and enhancement of kaliuresis during treatment with hydrochlorothiazide which is reversed by the administration of spironolactone.

dose of spironolactone or triamterine can be made intelligently. If the urinary concentration of potassium is high, the proper dose of spironolactone should increase the concentration of sodium as that of potassium falls.

Before concluding I would like to mention some of the complications of diuretics (Table 3). Except for spironolactone and triamterine, increased excretion of potassium is an almost invariable physiological consequence of diuretic agents. As was mentioned earlier, this effect is due to the increased delivery of sodium and water to the distal potassium secretory site and possibly to an effect of diuresis to simulate aldosterone output.[19,25] Potassium retention and hyperkalemia may complicate therapy with spironolactone or triamterine, agents that specifically interfere with potassium secretion.[23] The proper use of either of these drugs requires the frequent measurement of the serum potassium concentration. If edema or ascitic fluid is not mobilized in response to diuresis, then hypovolemia may be a major complication of diuretic therapy. Since edema or ascites may persist in the presence of an inadequate intravascular volume, diuretic-induced hypovolemia may not be readily apparent. However, during the course of diuretic therapy a fall in glomerular filtration rate (reflected by a rise in plasma creatinine or urea) and the retention of excess water (reflected by hyponatremia) should be regarded as signs of circulatory inadequacy and indications for discontinuing the diuretic agents.[19,26]

Disturbances of acid-base balance also may occur during treatment with diuretics. Acidosis will result from the use of a carbonic anhydrase inhibitor such as acetazolamide or early in the course of therapy with chlorothiazide.[18] Most of the other useful diuretics increase the excretion of chloride to an extent greater than that of

bicarbonate and as a consequence produce metabolic alkalosis.[26] Potassium depletion, by augmenting tubular hydrogen ion secretion, may contribute to alkalosis. The effect of thiazide diuretics to produce carbohydrate intolerance and worsen diabetes mellitus is familiar to most clinicians,[18] and it appears that furosemide also may have such an effect.[27] Hyperuricemia was originally described as a complication of the thiazide diuretics, but it also occurs with other diuretics. It appears that this may be a nonspecific consequence of diuresis and volume contraction to decrease urate clearance,[28] possibly as a result of enhanced tubular reabsorption.

Except in the case of organomercurials, nephrotoxicity has not been a complication of diuretic agents.[19] However, all diuretic agents, like other drugs, may be associated with sensitivity reactions manifested by hematological, dermatological, or vascular disorders. Pancreatitis has been produced experimentally in animals receiving high doses of certain combinations of thiazide diuretics, and the clinical disease also has been attributed to the agents.[18] When administered in high doses, usually intravenously, ethacrynic acid[29] or furosemide[30] may produce an acute nerve deafness, which appears in most instances to be reversible. Because of the number of potentially dangerous complications of diuretic therapy, the physician caring for patients receiving these drugs should be aware that some of these side effects may preclude achieving the degree of diuresis that may have seemed desirable.

DR. SLEISENGER: Dr. Earley, would you mention the treatment of chloride depletion when one attempts to restore sensitivity to diuretics?

DR. EARLEY: The hypochloremic alkalosis that occurs with diuretic therapy can be corrected by judiciously replacing some of the sodium chloride excreted. Also, other acidifying agents, such as arginine hydrochloride, may be used. Only organomercurials become ineffective in the presence of hypochloremic alkalosis and since we have powerful, orally effective agents, there may be little reason to use organomercurials. Mercurials are potentially nephrotoxic, require parenteral administration, and often cause cramps and other discomforts for the patient. The diuretic action of thiazides, ethacrynic acid and furosemide seems to be uninfluenced by hypochloremia or alkalosis.

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